

# VITAMIN K IN PRENATAL PREVENTION AND POSTNATAL TREATMENT OF HAEMORRHAGIC DISEASE OF THE NEWBORN

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Vitamin K is an essential in human nutrition for the maintenance of normal blood clotting function. It is involved in the synthesis of prothrombin and is directly related to the concentration of the latter in the circulating blood. We have (Kugelmass and Samuel, 1931) advanced the hypothesis of a dietary basis of the formation of clotting constituents, formulated 'clotting' and 'bleeding' diets (Kugelmass, 1935a), and applied these in the treatment of amenable haemorrhagic diseases (Kugelmass, 1934). The isolation of the poultry-feed factor in crystalline form (Dam and Lewis, 1937) as vitamin K by Almquist (1937) has led us to determine its effectiveness in haemorrhagic disease of the newborn characterized by diminution in blood prothrombin. This anti-haemorrhagic vitamin is a complex of  $K_1$  derived from vegetable and  $K_2$  derived from animal sources. The potency of each of these compounds has been determined by various methods of assay (Thayer et al., 1939). These data indicate that vitamin  $K_1$  is approximately twice as potent as  $K_2$ , the former about 1000 units per mgm. and the latter about 660 units. A unit of vitamin K is defined as that quantity which produces a clotting time of ten minutes or less in half a group of ten or more chicks which have been fed for two weeks immediately following a vitamin K-free dietary.

Vitamin K abounds in the unsaponifiable non-sterol fraction (Dam et al., 1936) of unsuspected sources such as alfalfa, beef liver, bran, breast milk, cabbage, casein, carrot tops, hog-liver oil, kale, mushrooms, peanut, pig-liver fat, rice bran, soy-bean oil, spinach and tomatoes, but is surprisingly absent in such foods as carrots, cereals, cod-liver oil, colostrum, corn, egg white, lemon juice, liver extract, mangoes, potato, rice, rye, wheat germ oil and yeast. This fat-soluble vitamin of dietary origin is absorbed in the intestinal tract in the presence of bile but is completely eliminated in the stool in its absence. Bile salts apparently combine with the vitamin hydrocarbon to enable its diffusion into the intestinal mucosa, otherwise its administration must be supplemented by bile salts, bile acids or desoxycholic acid. It has already been demonstrated that patients maintained on diets devoid of the vitamin for a fortnight

still show a large quantity in the lipid fraction of the stools as a result of the putrefactive processes by intestinal flora. But vitamin K is normally present in the stools in considerable amounts due to the relatively low efficiency of intestinal absorption.

The metabolism of vitamin K is unknown but its rôle in the synthesis of prothrombin in the bone-marrow and liver is established. The lipoid structures of these reticuloendothelial tissues utilize the fat-soluble vitamin to liberate prothrombin into the blood and lymph which are the immediate sources of this clotting component. Its origin is clear from the experimental studies of Drinker (1916), who obtained prothrombin from megakaryocytes by perfusion of marrow ; of Tait and Green (1926), who extracted prothrombin from platelets ; of Sanford (1938), who found prothrombin in disintegrated platelets ; and of Nolf (1921), who demonstrated the formation of prothrombin in the liver. Indeed, all protein-containing tissues yield the substances necessary for clotting the blood that may be shed through them, but only bone-marrow and liver liberate prothrombin in appreciable amounts into the circulation. Obviously any functional disorders of these tissues may interfere or arrest the formation of prothrombin and lead to the development of haemorrhagic manifestations due to prothrombin deficiency.

#### **Prothrombin concentration**

The prothrombin concentration in the blood of normal infants and children remains relatively constant under various conditions. Hundreds of estimations of blood clotting function have demonstrated that nutritional, metabolic, allergic, infectious and endocrine disorders of a non-haemorrhagic nature do not alter the functional level of blood prothrombin. It was determined as the prothrombin index (Kugelmass et al., 1930) which is the ratio of the clotting time of recalcified oxalated plasma of a control to that of a patient. The prothrombin time measured for each has been directly proportional to the active prothrombin concentration in the plasma and only indirectly affected by the concentration of other clotting components. Since this index gives only the intensity factor of immediate value in clotting and not the capacity factor of reserve value, we have also determined the prothrombin content by the method of Warner (1936) expressed in per cent. plasma level of normal children. The values obtained for all age groups after the first year of life are approximately similar and relatively constant in agreement with Brinkhous (1939). As soon as the blood volume has reached about one litre the level of prothrombin becomes that of adult blood.

The prothrombin level of the newborn is about a fourth of that in adult blood (Kugelmass, 1932). This apparent deficiency is not borne out by quantitative considerations, for normal blood contains over a hundred times the amount of prothrombin actually required for coagulation. On diluting the newborn's plasma a hundred times, sufficient thrombin is still produced to

clot fibrinogen within a minute, providing all other clotting components are present in normal amounts. On that basis a drachm of the newborn's blood has enough prothrombin to clot his entire volume of circulating blood while only five drachms of adult's blood will coagulate his total blood volume, although it is about twenty times that of the newborn. The ability of prothrombin to form thrombin is the same in the newborn as it is in the adult, for the clotting time at birth, directly proportional to prothrombin activity, is invariably within normal limits. The prothrombin content undersaturated in the blood of infants during the first few months of life may be increased by the administration of vitamin K in oil. Since there is normally sufficient reserve in prothrombin to fulfil the clotting functions of the newborn's blood, there is no indication to administer vitamin K routinely to bring the prothrombin levels to that of the adult blood. It is only when the prothrombin content of the newborn is diminished, or the clotting time increased, that vitamin K therapy is indicated as a preventive measure. But the reserve level of prothrombin of older infants and children is apparently unaffected by increasing vitamin K intake. An adequate diet thus provides sufficient vitamin K to produce considerably more than the necessary amount of prothrombin to arrest haemorrhage in normal infants and children.

#### **Vitamin K and the haemorrhagic disease**

This self-limited syndrome of unknown etiology occurs only within the first week of life. It is characterized by spontaneous haemorrhage, external or internal, in any tissue of the body excluding that associated with trauma, accident or other disease. The condition is relatively rare, and each case differs in the cause and course of its development, but the bleeding is invariably due to prothrombin deficiency in the blood.

I reported ten cases of haemorrhagic disease of the newborn, nine of which showed marked depression in the prothrombin content of the blood with a corresponding lowering in the clotting time (1935b). All other clotting factors were normal—bleeding time, clotting retraction, fibrinogen, antithrombin and platelets, although the rate of disintegration of the platelets was somewhat below normal in some of the cases. Since the determining factor in haemorrhagic disease of the newborn was consistently a decreased blood prothrombin, we designated this condition as acute hypothrombinaemia (Kugelmass and Tritsch, 1934).

The mild form of this disease is undoubtedly self-limited, for two of the ten cases were discovered in the course of routine clotting-time determinations. They showed the characteristic blood features and were treated promptly before bleeding developed. Apparently some cases of potential haemorrhagic disease of the newborn clear spontaneously and thus escape clinical recognition. But severe cases respond poorly to all forms of therapy in spite of diagnosis on the first day of life. These have been associated with prenatal transmission of

the disease indicated by the lowered prothrombin content of the expectant mother's blood.

Such a carefully controlled human experiment consisted of a mother who had given birth to four successive infants with fatal haemorrhagic disease confirmed by necropsies. The recognition of a low prothrombin content during her fifth pregnancy made it possible to bring this to normal levels by the administration of an adequate diet high in fat and protein, apparently abundant in the recently identified vitamin K. The fifth infant was normal and without haemorrhagic symptomatology to date. The sixth pregnancy was characterized by a similar decrease in the prothrombin level, but the mother refused nutritional therapy and gave birth to an infant with severe haemorrhagic disease. During her seventh pregnancy the prothrombin level was raised by adequate diet as during the fifth pregnancy and the infant was normal (Waddel and Guerry, 1939).

Several such cases have been observed with a history of haemorrhagic disease in a previous infant but with a normal blood prothrombin in the mother during the second pregnancy.

A clear-cut case, however, of prenatal prevention of potential haemorrhagic disease was that of an under-nourished woman who had given birth to a proven case of melaena. She was the only member of her family that had showed any bleeding tendency, for since the onset of her menstruation she had occasional nose bleeds, oozing from the gums and mild metrorrhagia and ecchymoses from easy bruising, diagnosed as David's disease. All these manifestations cleared, however, during the previous pregnancy and since the onset of the present pregnancy. At the third month examination of her blood showed a prothrombin index of 0.4, a prothrombin concentration of 30 per cent. and all other clotting components normal. The clotting time was 4 minutes, the bleeding time  $1\frac{1}{2}$  minutes, the tourniquet test negative, clotting retraction normal. The low prothrombin level was correlated with a limited dietary of a food faddist, apparently deficient in vitamin K. An accessory bacterial source of the vitamin from intestinal contents was also decreased by the persistent practice of colonic irrigation because of her abhorrence of alimentary toxæmia. An unstable blood clotting mechanism thus became susceptible to vitamin K deficiency, corrected by the administration of the extract in capsules with each meal and adjusting dietary regime to her individual requirements. This readjustment was met with some difficulty, hence the blood was not tested until the sixth month of pregnancy, when the prothrombin approached normal levels. At term, a normal male infant was born without the slightest evidence of haemorrhagic manifestations.

Two cases of haemorrhagic disease of the newborn were recently treated with vitamin K.

In the first case the mother was a primipara with an allergic migraine, maintained on a restricted diet low in protein and fat throughout her pregnancy. An apparently healthy male infant was born without instrumental delivery. On the second day he refused feedings, became restless, vomited dark brown material and showed continuous oozing from the cord. The clotting time was twenty-two minutes, prothrombin index 0.4, prothrombin percentage of normal plasma, twelve. Ten hours after the oral administration of 2 c.c. of vitamin K in oil the bleeding ceased and the clotting time was 10 minutes, prothrombin index 0.8 and prothrombin level 18 per cent.

In the second case the mother, also a primipara with chronic nephritis, was maintained on a restricted dietary low in vitamin K. A female infant born without instrumental delivery was apparently well until the third day, when she developed high fever, vomited after feedings and subsequently passed tarry stools. The clotting time was 17 minutes, prothrombin index 0.5 and prothrombin level 9 per cent. About eight hours after the oral administration of 3 c.c. of vitamin K in oil the bleeding ceased and the clotting time was 5 minutes, prothrombin index 0.7 and the prothrombin level 15 per cent.

Vitamin K administered to two mild cases of haemorrhagic disease of the newborn cleared the condition within twenty-four hours. There was a rise in blood prothrombin and a corresponding diminution in clotting time. Spontaneous bleeding ceased without resorting to other forms of local or systemic therapy more rapidly than expected of a self-limited condition. Vitamin K is thus of equal value with blood transfusion in mild cases, the one forming prothrombin and the other providing it. But mild cases of haemorrhagic disease of the newborn offer no final criteria of the curative value of vitamin K because the co-existence of haematogenous jaundice may diminish absorption and utilization of the vitamin and thus interfere with the synthesis of prothrombin. The ability of vitamin K to raise prothrombin to higher levels in the blood of the newborn is certainly no index of its efficacy in the presence of haemorrhagic disease characterized by injury to the reticuloendothelial system involved in the formation of prothrombin.

Vitamin K is nevertheless a valuable adjuvant in the treatment of latent or active haemorrhagic disease of the newborn. But therapy should not be limited to a precursor of prothrombin when the active substance can be injected into the circulation in the form of a blood transfusion. Certainly there is no indication for the use of vitamin K routinely to protect the newborn from possible haemorrhagic disease because there is ample prothrombin for clotting shed blood. Furthermore, abnormally high prothrombin content cannot prevent blood from oozing through a damaged vascular system unless the entire circulation is clotted! The contention (Kugelmass, 1933) that the prevention of haemorrhagic disease of the newborn will necessarily diminish intracranial haemorrhage is only partially true, because the former is a disease of the blood and the latter a result of trauma to the vascular system. A normal blood coagulability does not preclude vascular injury and vice versa. Besides, the relative frequencies of haemorrhagic disease and intracranial haemorrhage are about one to twenty and the two diseases are more often mutually exclusive than coexistent.

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